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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/032,972	02/26/98	KROTZ A	ISIS-2710

HM22/0207

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EXAMINER	
CRANE, L	
ART UNIT	**PAPER NUMBER**
1623	11

DATE MAILED: 02/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/032,972	Krotz et al.	
Examiner	Group Art Unit	
L. E. Crane	1623	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -----3---MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 11/22/99 (Amdt B)

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-41 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-41 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

No claims have been cancelled and the claim amendments filed November 22, 1999 have been entered.

Claims **1–41** remain in the case.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1–41** are rejected under 35 U.S.C. §103(a) as being unpatentable over Ravikumar '621 (PTO-892 ref. **A**) in view of Caruthers et al. '679 (PTO-892 ref. **G**) and further in view of Froehler et al. '076 (PTO-892 ref. **H**) and further in view of Sproat et al. (PTO-892 ref. **W**), Conway et al. (PTO-892 ref. **Y**), Atkinson et al. (PTO-892 ref. **Z**), and Sproat et al. (PTO-892 ref. **RA**).

The instant claims are directed to entirely conventional oligonucleotide syntheses wherein the only variation from the prior art is the choice of solvent or solvent mixture present for deprotection step (c).

Ravikumar '621 (PTO-892 ref. **A**) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 10, lines 1-16, this reference makes a generic disclosure of the process steps leading to an oligonucleotide, including acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more complete disclosure of possible 5'-hydroxyl protecting groups is provides along with a list of acids effect to deprotect, but no preferred solvents are listed. At column 18, lines 37-41, deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Caruthers et al. '679 (PTO-892 ref. **G**) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where <u>four</u> different solvent/reagent

systems were disclosed by Caruthers as effective in the 5'-O-detritylation process:
(1) see column 16, Table IV, footnote 1 ($ZnBr_2$ in nitromethane);
(2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));
(3) see column 18, lines 26-28 ($ZnBr_2$ in nitromethane:methanol (19:1)); and
(4) see column 19, lines 47-50 (80% acetic acid).
This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Froehler et al. '076 (PTO-892 ref. **H**) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof. This reference also teaches the use of " ... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This "what ever works best" philosophy apparently also applies to the deprotection step; see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Sproat et al. (PTO-892 ref. **W**) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene

is a solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

Conway et al. (PTO-892 ref. **Y**) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

Atkinson et al. (PTO-892 ref. **Z**) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

Sproat et al. (PTO-892 ref. **RA**).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and

reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

The teachings of the prior art Caruthers and Froehler references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates including the 5'-O-deprotection process step. The noted portions of the Caruthers and Froehler both teach that the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner. The Sproat et al. (W), Conway et al., Atkinson et al., and Sproat et al.(RA) references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references. The secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific motivations for the ordinary practitioner conducting routine

experimentation to substitute toluene, benzene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis. For these reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed November 22, 1999 have been fully considered but they are not persuasive.

Applicant has argued that "none of the references [of record] alone or in combination teaches or suggests the present invention," and concludes that the " ... Office Action has failed to establish a *prima facie* case of obviousness." Examiner respectfully disagrees. Applicant admits that the only variation over the prior art of record is the use of " ... aromatic solvents for the deprotection step." Caruthers teaches that the a number of different solvents are usable for acid-mediated 5'-hydroxyl deprotection. Additionally, after listing four different solvent/reagent alternatives, Froehler et al. also discloses a "whatever works" approach to deprotection. Although applicant is correct in stating that " .. none of the references cited ... teach or suggest the use of aromatic solvents for the deprotection step," examiner concludes that both Caruthers and Froehler grant a considerable degree of latitude to the ordinary practitioner in the selection of solvents and reagents for the 5'-O-deprotection step.

Therefore, examiner maintains the view that the prior art of record leaves the choice of solvent for the 5'-O-deprotection step in oligonucleotide synthesis within the purview of the ordinary practitioner seeking to optimize the prior art via routine experimentation. For this reason the instant rejection has been maintained.

The instant Office action has not been made final because of the substantial changes in the descriptions of the prelevant portions of the cited prior art.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592** .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639** . The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235** .

Art Unit 1623

LECrane:lec
02/04/00

L. Eric Crane
Patent Examiner
Group 1600